REVIEW AND EVALUATION OF PHARMACOLOGY/TOXICOLOGY DATA:

KEY WORDS: PCMX, ADME study, protocol review, topical antimicrobial, OTC antimicrobial, chloroxylenol
Reviewer Name: Terry S. Peters, D.V.M.
Division Name: Anti-Infective Drug Products
HFD #: 520
Review Completion Date: 11/8/00
IND/NDA number: OTC Docket #75N-183H
Serial number/date/type of submission: 8/22/00, ADME/protocol
Information to sponsor: Yes
Sponsor (or agent): NIPA Inc., Wilmington, DE
Contact person: Irving Gottlieb (302) 478-1522
Manufacturer for drug substance: NIPA Inc., Wilmington, DE

Drug:

Code Name: PCMX
Generic Name: Chloroxylenol
Chemical Name: Phenol,4-chloro-3,5-dimethyl-4-chloro-3,5-xylenol
CAS Registry Number: 88-04-0
Molecular Formula/ Molecular Weight: C_8H_9ClO; 156.61

Relevant INDs/NDAs/DMFs: NDAs 19128, 9004 and 1668

Drug Class: Inactive ingredient in topical antimicrobial

Indication: Antisepsis of skin

Route of administration: Topical

Studies reviewed within this submission:
1) **A 13-Week Dermal Toxicity Study of PCMX in Mice** (Protocol)
2) **Dermal Absorption with [14C]-Labeled PCMX in Mice** (Unaudited draft report)

Scientific literature reviewed: Yes
TOXICOLOGY:

Study Title: A 13-Week Dermal Toxicity Study of PCMX in Mice **(PROTOCOL REVIEW)**
Study No: WIL-30-4003
Vol #, and page #: 1, page 1
Conducting laboratory and location: WIL Research Laboratories, Ashland, OH
Date of study initiation: To be determined
GLP compliance: Yes
QA- Report: Yes
Methods:
Dosing:

- species/strain: CD-1 mice
- #/sex/group or time point: 3/sex/group for the acute test except 4/sex/group for the 24 hour time point; 4/sex/group for the repeat dose testing, either 14 or 28 days.
- age: 6 weeks at study initiation
- weight: 20-30 gms
- satellite groups used for toxicokinetics or recovery: none
- dosage groups in administered units: 0 (naïve control, vehicle control [acetone]), 100, 333 or 1000 mg/kg/d
- route, form, volume, and infusion rate: Topical at 50 µL/mouse/day for 13 weeks

Drug, lot: To be determined
Formulation/vehicle: Acetone

Observations and times:

- Clinical signs: Twice/day for mortality/morbundity, once/day (3 hours post-dosing) for dose-related signs, once/week for dermal signs, behavioral signs and changes in appearance
- Body weights: Weekly
- Food consumption: Weekly
- Ophthalmoscopy: Pre-dosing and "near the end of the dosing period".
- EKG: Not performed
- Hematology: At the end of the dosing period from 5/sex/group from control and high dose only. If platelet effects are noted, the evaluation will be extended to the other groups. To appropriately evaluate any potential treatment-related effects, all animals from control and high dose groups should be examined. The remaining animals should be examined if effects are noted.
- Clinical chemistry: At the end of the dosing period from 5/sex/group. To appropriately evaluate any potential treatment-related effects, all animals from control and high dose groups should be examined. The remaining animals should be examined if effects are noted.
- Urinalysis: Not performed. Urine collected for radioactivity evaluation only.
- Gross pathology: All animals
  - Organs weighed: Adrenals, brain, epididymides, heart, kidneys, liver, ovaries, spleen, testes, thyroid, thymus, uterus
- Histopathology: All tissues listed below from control and high dose animals and skin and gross lesions from all others. Animals killed in extremis or found dead will be examined histologically. It is recommended that any target tissues identified in the high dose animals be examined from all animals. Special attention should be paid to kidney and liver based upon the PK study reviewed below.

Histopathology Inventory for IND #

Adrenals	X
Aorta	X
Bone Marrow smear	X
Bone (femur)	X
Brain	X
Cecum	X
Cervix	X
Colon	X
Duodenum	X
Epididymis	X
Esophagus	X
Eye	X
Gall bladder	X
Gross lesions	X
Harderian gland	X
Heart	X
Ileum	X
Jejunum	X
Kidneys	X
Liver	X
Lungs	X
Lymph nodes, mesenteric	X
Mammary Gland (females only)	x
Ovaries	X
Pancreas	X
Parathyroid	X
Peripheral nerve	X

Pituitary	X
Prostate	X
Rectum	X
Salivary gland	X
Sciatic nerve	X
Seminal vesicles	X
Skeletal muscle	X
Skin	X
Spinal cord	X
Spleen	X
Sternum	X
Stomach	X
Testes	X
Thymus	X
Thyroid	X
Tongue	X
Trachea	X
Urinary bladder	X
Uterus	X
Vagina	X

Study Title: **A Dermal Absorption Study with [14C]-labeled PCMX in Mice**
Study No: WIL-304002
Vol #, and page #: 1, page 1
Conducting laboratory and location: WIL Research Laboratories, Ashland, OH
Date of study initiation: 9/22/99
GLP compliance: Yes
QA- Report: Yes
Methods:
Dosing:

- species/strain: CD-1 mice
- #/sex/group or time point: Single dose: 3/sex/dose/time point; Repeat dose: 4/sex/dose/timepoint for 14 or 28 days
- age: 7 weeks at study initiation
- weight: Males: 18.8- 31.0 gms; females: 14.6- 29.2 gms
- satellite groups used for toxicokinetics or recovery: none
- dosage groups in administered units: 2.4, 8.0 or 24 mg/dose as a single or repeat dose regimen with 5 μCi of ^{14}C/dose. Actual mean doses were determined for the single dose test to be 2.5, 8.7, 25, and 23 mg/mouse and for the repeat dose test to be 2.5, 8.3 and 25 mg/dose.
- route, form, volume, and infusion rate: Topical at 40 μL/mouse

Drug, lot: Batch E22-1 (unlabeled PCMX) and 990809 (labeled PCMX)
Formulation/vehicle: Acetone or DMSO (highest dose only for the single dose group)
Procedure: For the single dose test, the doses were applied and urine and feces were collected thereafter. For the acetone vehicle animals, 3/sex/dose were euthanized at 3, 6, 12 and 48 hours after dosing. Skin from the dose site and a blood sample were taken from each animal. At 24 hours after dosing, 4/sex (high dose group only with DMSO as the vehicle) were euthanized and liver, kidney, brain and tongue were analyzed for radioactivity. The carcasses were also retained for analysis. Urine and feces were collected once from each animal.

For the repeat dose test, 4/sex/dose were dosed daily for 14 or 28 days with urine and feces collected for 24 hour periods until the final dose. Animals were euthanized 24 hours after the final dose.
Observations and times:

- Clinical signs: Not performed
- Body weights: Not performed
- Food consumption: Not performed

- Ophthalmoscopy: Not performed
- EKG: Not performed
- Hematology: Not performed
- Clinical chemistry: Not performed
- Urinalysis: Not performed
- Gross pathology: Not performed
- Organs weighed: Not performed
- Histopathology: Not performed

Results: Radioactivity recovery ranged from 38.9% to 88.8% in males and 36.7% to 92.6% in females. Mean recovery for both sexes was ~65%. The explanation offered by the sponsor is that the test article and/or a metabolite are volatile and the methodology was not designed to recover any volatile components.

Absorption increased with increasing length of exposure (single dose test). The percent of dose absorbed was higher after 14 days of dosing than after a single dose, but did not increase further after 28 days of dosing. Approximately 50% of the dose was absorbed after 24 hour exposure, and approximately 65% after 28 days of repeat dosing. Some of the dose remained in the skin and was higher after 14 days of dosing than after the single dose. With DMSO used as the vehicle, the % in the skin was ~4x lower than when acetone was used as the vehicle.

Absorption proceeded in a biphasic fashion. At 2.4 mg, the initial phase was 3-6 hours in males, and 3-12 hours for females. At 24 mg, the initial phase was from 3-24 hours for both sexes. The results indicate a possible limitation to absorption at the high dose with no evident saturation at any dose.

Absorption through the skin was noted at all time points with the highest amounts of PCMX at 3 hours (~15% at the lowest dose, lower at higher doses) post-dosing. Absorption decreased with increasing dose duration. At the lower doses, the elimination rate was 0.1-0.2/hr. At the high dose, elimination appeared to be monophasic but proportional to dose at 3 and 48 hours after dosing.

For males, the t ½ for PCMX in skin was 47, 44 and 8.5 hrs for low-high dose groups, respectively, and for females, 27, 14 and 8.5 hrs, respectively.

An interesting finding was that measurable amounts of radioactivity were found in the plasma at all time points while mean concentrations for the cellular components of blood (highly variable) were below the levels of quantitation for low and mid dose groups at 3 and 48 hours post-dosing. After the single dose, the PCMX in plasma was highest at 3 hours post-dosing and decreased with length of exposure. Initial concentrations were higher for females than males. The concentration of PCMX in plasma was proportional to dose at 3 and 48 hours post-dosing. For males, the t ½ in plasma was 18, 22, and 12 hours and for females, 70, 9.1 and 12 hours, respectively. No vehicle effects were reported for plasma levels as were reported for the skin.

Tissue concentrations were highest in kidney> liver> brain and increased between Days 1 and 14. Concentrations in the tongue continued to increase over the repeat dosing period, suggesting oral ingestion through self-grooming. When DMSO was used as the vehicle, less absorption into tissues was reported.

Radioactivity was eliminated primarily in the urine with the majority of the dose eliminated within 24 hours of dosing (~70% for males, ~65% for females). Approximately 3% of the dose was eliminated in feces. Elimination rate constants were t ½ of ~ 10 hrs. for males, and ~8.6 hrs. for females. Fecal elimination rates were significantly longer (15-50 hrs).

RECOMMENDATIONS:

Internal comments: Since approximately 50% of the dose appears to be absorbed through the skin of mice, carcinogenicity studies with PCMX should be conducted at doses providing significant multiples of the proposed human dose.

External Recommendations (to sponsor): Since approximately 50% of the dose appears to be absorbed through the skin of mice, carcinogenicity studies with PCMX should be conducted at doses providing significant multiples of the proposed human dose.

Reviewer signature: Jerry S. Peters, D.V.M.

cc: list
HFD-560/Orig. docket
HFD-520/PT/Peters
HFD-520/CSO/Dillon-Parker
Draft date (# of drafts): 11/8/00; #1

Concurrence Only:
HFD-520/DepDivDir/Gavrilovich 12/4/00
HFD-520/PTTeamLdr/Osterberg 12/1/00

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 8.2.02

FROM: Director
Division of OTC Drug Products, HFD-560

SUBJECT: Material for Docket No. 75N-183H

TO: Dockets Management Branch, HFA-305

[X] The attached material should be placed on public display under the above referenced Docket No.

[X] This material should be cross-referenced to Comment No. PR8 + PR3

Charles J. Ganley, M.D.

Attachment